Narrative Review

The Therapeutic Potential of Theobromine in Obesity: A Comprehensive Review

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Obesity, characterized by chronic low-grade inflammation, is a significant health concern. Phytochemicals found in plants are being explored for therapeutic use, particularly in combating obesity. Among these, theobromine, commonly found in cocoa and chocolate, shows promise. Although not as extensively studied as caffeine, theobromine exhibits positive effects on human health. It improves lipid profiles, aids in asthma treatment, lowers blood pressure, regulates gut microbiota, reduces tumor formation, moderates blood glucose levels, and acts as a neuroprotective agent. Studies demonstrate its anti-obesity effects through mechanisms such as browning of white adipose tissue, activation of brown adipose tissue, anti-inflammatory properties, and reduction of oxidative stress. This study aims to suggest theobromine as a potential therapeutic agent against obesity-related complications.

Key words: *theobromine, obesity, browning, anti-inflammatory, antioxidant.*

INTRODUCTION

Caffeine, theophylline, and theobromine are methylxanthines commonly encountered in our daily diet through the intake of cocoa, coffee, chocolate, and various teas. These constituents are widely regarded as safe for consumption.[1,2] Although theobromine (3,7-dimethylxanthine) has not been studied as extensively as caffeine, it has been reported to have positive effects on human pathology.[1] The primary sources of theobromine are cocoa (*Theobroma cacao*) and cocoa-based products such as chocolate. In 50 g of chocolate, there are approximately 19 mg of caffeine and 250 mg of theobromine.[3,4] The beneficial outcomes of cocoa on health have been broadly studied for many years. Specifically, emphasis has been placed on its potential benefits in hypertension,[5] cancer,[6] inflammatory conditions,[7] regulation of intestinal microbiota,[8] improvement of lipoprotein profile,[5,9] and the treatment and prevention of hyperglycemia and insulin resistance.[10] To our knowledge, there is no study indicating the toxicity of theobromine in humans, and in many instances, its potential positive impact on health are noted.[3] Theobromine plays a role in improving serum lipoprotein profile,[9,11,12] treating asthma and other respiratory tract diseases,[3] lowering blood pressure,[13] regulating gut microbiota,[8] reducing tumor formation,[14] regulating blood glucose levels,[12,15] and acting as a neuroprotective agent.[16,17] The anti-obesity effect of theobromine has been demonstrated in both in vitro and in vivo studies.[1,18,19] Possible mechanisms underlying this effect include the browning of white adipose tissue (WAT), activation of brown adipose tissue (BAT),[1,18] anti-inflammatory properties,[9,16,17,20–23] and reduction of oxidative stress.[16,17,20,24] Upon investigating the potential mechanisms of action of theobromine on obesity, no review addressing this topic has been found. The aim of this review is to fill the current gap in the literature regarding the effects and potential mechanisms of action of theobromine on obesity.

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METHODS

This review was structured as a narrative review to encompass all available research on theobromine extensively. The investigation used a comprehensive search across multiple databases, including PubMed, Web of Science, ScienceDirect, Google Scholar, and Scopus, accessed through the Hacettepe University Library. Keywords used to conduct the search were "theobromine" in combination with "obesity," "browning," "anti-inflammatory," and "antioxidant." Human and animal studies examining the effects of theobromine on obesity-related parameters in vivo and in vitro were included. Studies lacking primary data or presenting outcomes irrelevant to obesity were excluded. No temporal restrictions were imposed as exclusion criteria, to ensure a thorough coverage of the topic. A potential limitation of our search strategy is the reliance on English-language publications, which may have resulted in the exclusion of pertinent research published in other languages.

THEOBROMINE AND OBESITY

Obesity prevalence is increasing steadily, and it is now recognized as a global pandemic and a chronic disease.[25] According to the World Obesity Atlas 2023,[26] 38% of the global population was overweight or obese, and it is expected that this figure will rise to 51% by the year 2035. Although obesity results from a chronic positive energy balance, additional central and peripheral mechanisms regulating energy homeostasis play a role in its development.[27] The excessive number of adipocyte cells and increased adipocyte size in adipose tissue contribute to the development of obesity.[19] The increase in inflammatory adipokines associated with obesity results in the development of both insulin resistance and adipogenesis.[28] Obesity is closely associated with numerous comorbidities, including hypertension,[29] type 2 diabetes mellitus,[30] coronary artery diseases,[31] dyslipidemia,[32] nonalcoholic fatty liver disease,[33] chronic kidney disease,[34] polycystic ovary syndrome,[28] respiratory tract diseases, and malignancies.[35] The prevalence of these disorders is increasing steadily alongside obesity.[36] In addition to the adverse health effects of obesity, it is noted that annual healthcare expenditures increase by approximately 37% when the body mass index exceeds 30 kg/m^2.[25] Understanding the molecular mechanisms between obesity and chronic metabolic diseases has become increasingly important since the recognition of the inadequacy of dietary and behavioral changes in combating obesity in recent years.[9]

Phytochemicals found in plants and herbal products are being increasingly investigated for their potential therapeutic use in the treatment of various illnesses, and they are emerging as an area of growing interest in the context of combating obesity.[37] The positive effects of cocoa on body weight have been demonstrated in numerous studies.[7,9,38,39] High frequency of chocolate consumption in adults has been associated with lower body mass index,[27] and, in adolescents, it has been noted to be associated with lower fatness.[28] The effect of cocoa on body weight may stem from its positive impact on adipogenesis,[39] insulin resistance,[7] lipolysis and mitochondrial biogenesis,[40] and browning,[41] as well as its beneficial effects on oxidative stress and cortisol levels.[10]

It is emphasized that the positive effect of cocoa on obesity may be attributed to the presence of theobromine in its composition.[9] Despite the established benefits of theobromine, there remain significant gaps in understanding its specific mechanisms of action in obesity management. This review aims to address these gaps. Theobromine reduces body weight gain.[8,9,18,19,42] In vitro (Table 1)[1,18–24,42,43] and in vivo (Table 2)[9,12,16–19,24,42,44] studies indicate that theobromine is an effective phytochemical in combating obesity, and further research in this area is warranted. Theobromine can exhibit this effect by stimulating browning, increasing lipolysis-reducing adipogenesis, and through its anti-inflammatory effects (Figure 1).[1,9,16–19,21–23,42,43] Overall, although in vitro and in vivo studies play crucial roles in scientific inquiry, they constitute only partial evidence. To formulate evidence-based recommendations, incorporating findings from diverse studies, such as human clinical trials, systematic reviews, and meta-analyses, is essential for a comprehensive understanding of intervention effectiveness and safety.

Adipogenesis is the process whereby adipocytes generate and accumulate as adipose tissue, serving as both subcutaneous fat tissue and storage throughout various regions of the body.[45] Controlling adipogenesis is an effective strategy in preventing and treating obesity.[43] Adipocyte differentiation and adipogenesis are regulated by transcription factors, including members of the CCAAT/enhancer binding protein (C/EBP) family (C/EBPα, C/EBPβ, and C/EBPγ) and PPAR.[19] Theobromine can inhibit adipocyte differentiation by activating AMP-activated protein kinase and suppressing extracellular signal-regulated kinase and c-Jun N-terminal kinase signaling pathways.[23] Additionally, theobromine reduces the expression of PPARγ and C/EBPα genes.[19,23]

Theobromine and Browning

When the development of obesity is examined, it is evident that it is not solely dependent on the balance between food intake and energy expenditure. It is also dependent on the balance between WAT, the main

Table 1. Studies Investigating the In Vitro Effect of Theobromine on Obesity

In vitro effect	Sample/model	Theobromine dose	Duration	Results	Reference
Browning	3T3-L1 white adipocytes and HIB1B brown adipocytes	0-200 μM	6–8 d	3T3-L1: Expression levels of beige-specific genes (Cidea, Cited1, Tbx1, and Tmem26) ↑ Expression levels of brown-specific genes (Ppargc1α, Prdm16, and Ucp1) ↑ Adipogenesis ↓ Lipolysis ↑ H1B1B: Expression levels of brown fat–specific genes (Cidea, Eva1, Lhx8, Ppargc1, Prdm16, Ucp1, and Zic1) ↑ Brown-fat signature proteins (PGC-1α, PRDM16 and UCP1) ↑	Jang et al (2018)[1]
Browning	3T3-L1 white adipocytes and HIB1B brown adipocytes	200 μM	6–8 d	3T3-L1 and H1B1B: PDE4D expression ↓ Induced browning	Jang et al (2020)[18]
Browning	Adipose stromal cells were isolated from inguinal WAT of mice	5 μM	7 d	Expression levels of Ppargc1a gene slightly ↑	Tanaka et al (2022)[42]
Adipogenesis	3T3-L1 preadipocytes	0.50, 100, and 150 μg mL^{-1}	7 d	Inhibition of adipocyte differentiation Downregulation of PPARγ, C/EBPα, aP2, and leptin Suppression of the early stage of adipogenesis AMPK phosphorylation ↑ ERK and JNK signaling pathways suppression	Jang et al (2015)[23]
Adipogenesis	3T3-L1 preadipocytes	25 μM	8 h or 6 d	Suppressed protein expression of PPARγ, C/EBPα and adipogenic genes ↓ Suppressed adipogenesis	Mitani et al (2017)[19]
Adipocyte differentiation	SGBS cells (human preadipocytes)	100 μg mL^{-1}	6 d	Inhibition of adipocyte differentiation	Fugetta et al (2019)[43]
Anti-inflammation	3T3-L1 preadipocytes	50, 100, and 150 μg mL^{-1}	7 d	TNF-α and IL-6 production ↓	Jang et al (2015)[23]

(continued)

Table 1. Continued

In vitro effect	Sample/model	Theobromine dose	Duration	Results	Reference
Anti-inflammation	dSGBS adipocyte cells Human dU937 macrophages Cocultured dSGBS adipocyte cells with DU937 macrophages (10:1)	100 μg mL^{-1}	48 h	dSGBS adipocyte cells: levels of MCP-1 and IL-1β ↓ Human dU937 macrophages: levels of IL-1β ↓ Coculture of dSGBS and dU937: levels of MCP-1 and IL-1β ↓	Fugetta et al (2019)[43]
Anti-inflammation	RAW 264.7 macrophages cell line	0.1–25 μg mL^{-1}	24 h	Upregulated TNF-α and IL-6 levels Increase the activation of NF-κB Induced NO and PGE2 production MAPK phosphorylation ↑	Lee et al (2022)[67]
Anti-inflammation	U87-MG human glioblastoma cells	0–10 μM	72 h 10 min	ERK inhibition MAPK and JNK phosphorylation ↑ NF-κB phosphorylation ↓	Sugimoto et al (2019)[22]
Anti-inflammation	Human colorectal adenocarcinoma CaCo-2 cells	10 μM	1 h	IL-8 and MCP-1 protein levels ↓	Iaia et al (2020)[21]
Anti-inflammation	SW1353 cell line	25 and 50 μM	48 h	Suppressed the induction of PGE2 and COX-2 NO production ↓ Induction of TNF-α and MCP-1 ↓ Suppresses cellular NF-κB activation	Gu et al (2020)[20]
Antioxidation	SW1353 cell line	25 and 50 μM	48 h	Suppression of ROS production	Gu et al (2020)[20]
Antioxidation	Immortalized human mesangial cells	44 nM	24 h	ROS formation ↓	Papadimitriou et al (2015)[24]

Abbreviations: AP2, adipocyte fatty acid binding protein; AMPK, AMP-activated protein kinase; C/EBPα CCAAT/enhancer binding protein α; Cidea, gene encoding cell-death inducing DFFA-like effector a; Cited1, gene encoding Cbp/p300-interacting transtivator 1; COX-2, cyclooxygenase 2; ERK, extracellular signal-regulated kinase; Eva1, gene coding myelin protein zero like 2; IL, interleukin; JNK, c-Jun N-terminal kinase; Lhx8, gene encoding LIM/homeobox protein Lhx8; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor kappa B; PDE4D, phosphodiesterase 4D; NO, nitric oxide; PGC-1α, PPARγ coactivator 1α; PGE2, prostaglandin E2; Ppargc1α, gene encoding peroxisome proliferator-activated receptor gamma co-activator 1-alpha; Prdm16, gene encoding PR domain containing 16; PRDM16, PR domain containing 16 [protein]; ROS, reactive oxygen species; Tmem26, gene encoding transmembrane protein 26; Tbx1, gene encoding T-box protein 1; TNF-α, tumor necrosis factor-α; Ucp1, gene encoding uncoupling protein 1; UCP1, uncoupling protein 1; Zic1, gene encoding zinc finger protein ZIC1.

Table 2. Studies Investigating the In Vivo Effect of Theobromine on Obesity

In vivo effect	Sample/model	Dose/application	Duration	Results (TB treated)	Reference
Browning	C57BL/6 mice fed an HFD and treated with or without theobromine	100 mg kg^{-1}, oral gavage	8 wk	Expression levels of PDE4D ↓ iWAT: expression levels of browning marker protein ↑ (PRDM16 and UCP1) BAT: BAT activation; brown fat–specific proteins and genes upregulated (Ppargc1α, Prdm16, Cidea, Eva1, Lhx8, Ucp1, and Zic1)	Jang et al (2020)[18]
Browning	C57BL/6N mice treated with or without theobromine	0–0.1%, oral	63 d	iWAT: expression of UCP1 protein ↑; expression of Ucp1 and browning-associated genes (Elovl3, Cidea, Cox7a1, Cox8b, and Cpt1b) ↑	Tanaka et al (2022)[42]
Adipogenesis	ICR mice received theobromine or vehicle alone	0.1 g kg^{-1}, oral gavage	7 d	Epididymal adipose tissue: expression of PPARγ, C/EBPα, and adipogenic proteins ↓; suppressed adipogenesis	Mitani et al (2017)[19]
Anti-inflammation	Lewis rats fed a standard diet, cocoa powder, or theobromine diet	0.25%, oral	7 d	Liver IL-10 and IL-1β mRNA levels ↓ Hepatic TNF-α and NF-κB expression ↑ Expression of MCP-1 in adipose tissue ↑	Camps-Bossacoma et al (2019)[9]
Anti-inflammation	Wistar rats	50 and 100 mg kg^{-1}, oral	7 d	Reduction of brain TNF-α and NF-κB levels	Bhat et al (2021)[16]
Anti-inflammation	Wistar rats	50 and 100 mg kg^{-1}, oral	14 d	Reduction of brain TNF-α, IL-1β, IL-6, and NF-κB	Bhat and Kumar, (2022)[17]
Anti-inflammation	Sprague Dawley rats received normal chow with or without theobromine	0.5 and 30 mg d^{-1}, oral	5 mo	No change in the level of IL-1β	Mendiola-Precoma et al (2017)[44]
Antioxidation	Wistar rats	50 and 100 mg kg^{-1}, oral	7 d	Brain GSH levels ↑ Dose-dependent decline in TBARS	Bhat et al (2021)[16]
Antioxidation	Wistar rats	50 and 100 mg kg^{-1}, oral	14 d	GSH, SOD, and catalase activity ↑ Lipid peroxidation ↓	Bhat and Kumar, (2022)[17]
Antioxidation	Spontaneously hypertensive rats (SHR) receive no treatment or treatment with theobromine	5 mg kg^{-1} d^{-1}, oral	12 wk	Ameliorated nitrosative stress-and oxidative stress-induced DNA damage ROS formation ↓	Papadimitriou et al (2015)[24]
Anti-inflammation	Middle-aged, overweight, and slightly obese men and women	500 mg d^{-1}, oral	4 wk	high-sensitivity C-reactive protein ↑	Smolders et al (2018)[12]

Abbreviations: BAT, brown adipose tissue; C/EBPα CCAAT/enhancer binding protein α; Cidea, gene encoding cell-death inducing DFFA-like effector a; Cpt1b, gene encoding carnitine palmitoyltransferase I; Cox7a1, gene encoding cytochrome c oxidase subunit VIIa polypeptid; Cox8b, gene encoding cytochrome C oxidase subunit 8 b; Eva1, gene coding myelin protein zero-like 2; Elovl3, gene encoding elongation of very-long-chain fatty acid-3; GSH, glutathione; IL, interleukin; Lhx8, gene encoding LIM/homeobox protein Lhx8; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor kappa B; PDE4D, phosphodiesterase 4D; Ppargc1α, gene encoding peroxisome proliferator-activated receptor γ co-activator 1-α; Prdm16, gene encoding PR domain containing 16; PRDM16, PR domain containing 16 [protein]; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TNF-α, tumor necrosis factor-α; UCP1, uncoupling protein 1; Ucp1, gene encoding uncoupling protein 1; iWAT, inguinal white adipose tissue; Zic1, gene encoding zinc finger protein ZIC1.

energy source, and BAT, which leads to energy expenditure through thermogenesis.[18] BAT provides protection against hypothermia and obesity by activating nonshivering thermogenesis through mitochondrial uncoupling protein-1 (UCP1).[46,47] The β-3 adrenergic receptor (β3AR) is the primary receptor involved in the metabolic pathway of thermogenesis.[48]

Although the number of brown adipocytes in BAT decreases after the neonatal period, there are beige or brite (brown-in-white) adipocytes in WAT that share

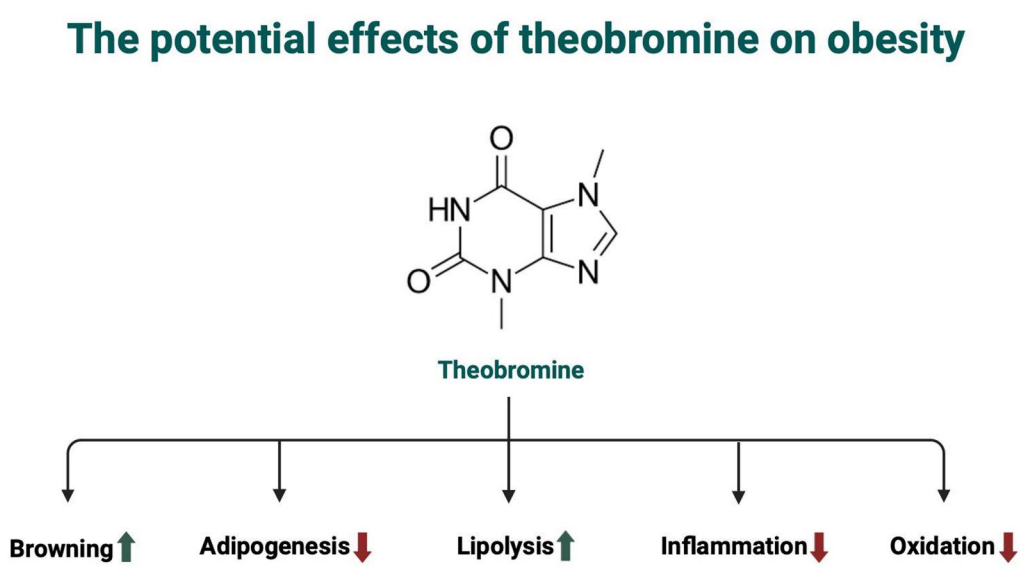

Figure 1. The Potential Effects of Theobromine on Obesity

morphological and biochemical characteristics with brown adipocytes.[42] Under basal conditions, beige adipocytes exhibit white adipocyte characteristics, but when there is sufficient stimulation, a process of morphological and histochemical browning occurs.[47] Browning is defined as any significant increase in UCP1 mRNA levels in regions typically considered as WAT, and this increase is closely associated with β3AR stimulation.[49,50] All PPAR isoforms (α, β, and γ) are closely associated with UCP1 transcription.[48] To initiate the process of browning, the transcription factor PR domain containing 16 (PRDM16), which interacts with PPARγ coactivator 1α and C/EBPβ, is required.[51] PRDM16 ensures the continuity of the beige adipocyte phenotype and also influences the process of browning. Even when PRDM16 expression is low, brown adipocytes can sustain thermogenesis, but, with reduced stimulation they can revert to white adipocytes.[48] Stimulation of a BAT-like phenotype in adipocytes is characterized by the generation of new mitochondria, upregulation of specific thermogenic genes, and increased free fatty acid β-oxidation. This represents a new approach in reducing obesity.[41]

It was discovered in the 1980s that exposure to cold results in parametrial adipose tissue stores exhibiting brown fat–like characteristics.[52] Exposure to cold induces sympathetic stimulation, resulting in both activation and growth of BAT.[53] It is noted that 63 g of fully activated BAT can burn approximately 4.1 kg of adipose tissue per year.[54] It since has been discovered that along with exposure to cold, there are many factors that induce browning, including phytochemicals,[55] exercise,[56] and pharmacological agents.[57]

Although the effects of phytochemicals found in the structure of cocoa on browning have been examined in different studies,[41,58] the impact of theobromine on browning has not been extensively studied. Theobromine stimulates the browning of white adipocytes by activating β3AR.[1] Activated β3AR leads to the activation of protein kinase A and AMP-activated protein kinase signaling pathways, thereby activating thermogenesis, while also inhibiting phosphodiesterase 4D, which prevents the conversion of adenosine triphosphate to AMP. As a result, energy expenditure is increased.[1,18,42] Theobromine increases the expression of with PPARγ coactivator 1α, PRDM16, and UCP1 proteins while enhancing the expression of beige-specific genes elongation of very-long-chain fatty acids-3, cell-death inducing DFFA-like effector a (Cidea), Cbp/p300-interacting transtivator 1, cytochrome c oxidase subunit VIIa polypeptid, coficytochrome C oxidase subunit 8 b, carnitine palmitoyltransferase I, transmembrane protein 26, and T-box protein 1 in white adipocytes; and brown-specific genes peroxisome proliferator-activated receptor γ co-activator 1-α, Prdm16, Cidea, the gene coding myelin protein zero-like 2, LIM/homeobox protein Lhx8, Ucp1, and zinc finger protein ZIC1 in brown adipocytes (Figure 2).[1,18,42]

In light of all these effects, it should be noted that theobromine stimulates browning; with further studies, its mechanism of action can be better understood, potentially positioning it as an effective "browning agent" in combating obesity. Given the promising outcomes, theobromine warrants consideration for inclusion in dietary interventions targeting the promotion of browning of WAT. Nevertheless, clinical trials are imperative to validate these findings and ascertain appropriate dosages.

Theobromine and Anti-Inflammatory Effect

Metabolic processes such as endoplasmic reticulum stress, hypoxia, and lipotoxicity, which can be stimulated by

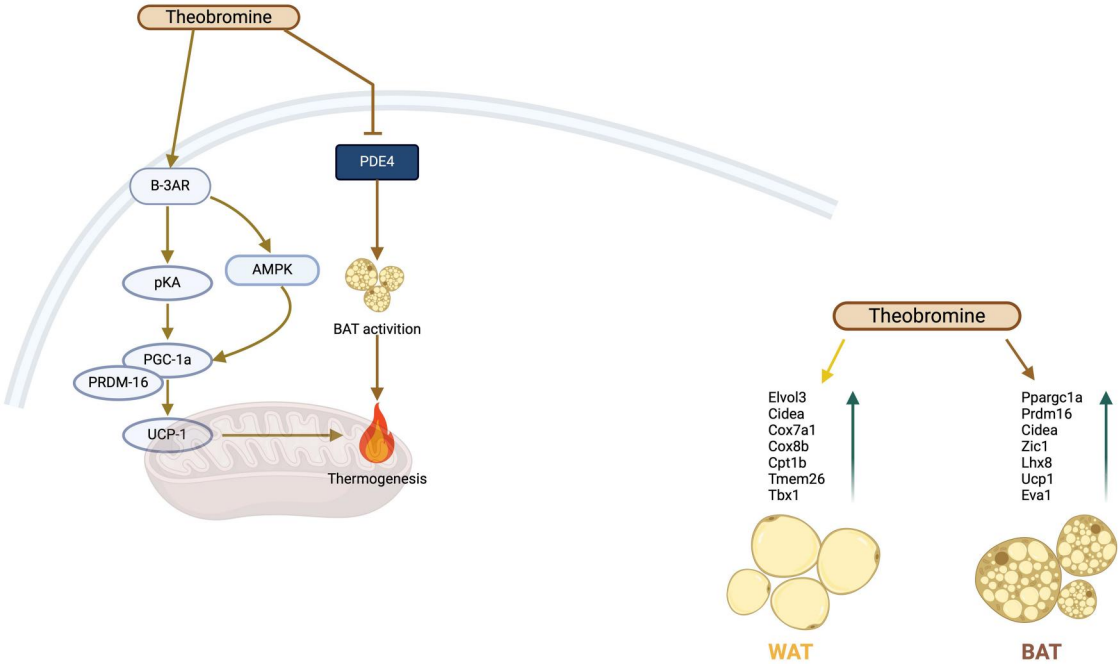

Figure 2. Potential Mechanism of Action of Theobromine on Browning. Abbreviations: β3AR, β-3 adrenergic receptor; AMPK, AMP-activated protein kinase; BAT, brown adipose tissue; Cidea, gene encoding cell-death inducing DFFA-like effector a; Cox7a1, gene encoding cytochrome c oxidase subunit VIIa polypeptid; Cox8b, gene encoding cytochrome C oxidase subunit 8b; Cpt1b, carnitine palmitoyltransferase 1B; Eva1, gene coding myelin protein zero-like 2; Elovl3, gene encoding elongation of very-long-chain fatty acid-3; Lhx8, gene encoding LIM/homeobox protein Lhx8; PDE4D, phosphodiesterase 4D; PGC-1α, PPARγ coactivator 1α; pKA, protein kinase A; Ppargc1α, gene encoding peroxisome proliferator-activated receptor γ co-activator 1-α; Prdm16, gene encoding PR domain containing 16; PRDM16, PR domain containing 16 [protein]; Tmem26, gene encoding transmembrane protein 26; Tbx1, gene encoding T-box protein 1; UCP1, uncoupling protein 1; Ucp1, gene encoding uncoupling protein 1; WAT, white adipose tissue; Zic1, gene encoding zinc finger protein ZIC1

excessive nutrient intake and adiposity, can lead to the development of metabolic inflammation.[59] Consuming an especially high-fat diet activates genes related to inflammation.[60] In 1993, it was documented that the release of an inflammatory cytokine called tumor necrosis factor-α (TNF-α) in the adipose tissues of obese mice was higher compared with in lean mice, which could potentially cause insulin resistance.[61] Subsequent studies have revealed that along with obesity, there is an increase in the number of macrophages infiltrating adipose tissue, and these infiltrated macrophages play an important role in the inflammation of adipose tissue.[62,63]

In the case of obesity resulting from increased food intake, there is an increase in nutrient stores within adipocytes. However, as the storage capacity is eventually exceeded, cell death occurs in a small portion of cells. This leads to the infiltration of macrophages into adipose tissue to clear the dead cells, and new adipocytes start to develop for the storage of excess nutrients. Continued excessive food intake results in more cell death, prompting macrophages to activate the adaptive immune system.[64–66] Stimulated macrophages induce inflammatory activity directly by causing the release of various cytokines and nitric oxide.[67] Control of adipogenesis can reduce lipid content in adipocytes and regulate the production of cytokines and chemokines, thereby regulating inflammatory response. This can be effective in preventing and treating obesity.[43]

Adipose tissue contains 2 distinct macrophage phenotypes: the alternatively activated pro-inflammatory macrophage phenotype (M1), or classically activated macrophages; and the anti-inflammatory macrophage phenotype (M2), or alternatively activated macrophages. These 2 macrophage types differ from each other both phenotypically and functionally. In diet-induced obesity, the M2 macrophage type present in adipose tissue transforms into the M1 macrophage type. This exacerbates the low-grade chronic inflammation observed in obesity.[43,66] Adipose tissue macrophages secrete cytokines and chemokines beyond TNF-α, including interleukin-6 (IL-6), IL-1β, monocyte chemotactic protein-1, and macrophage inhibitory factor.[59] The production of these factors occurs under the transcriptional control of 2 pathways: (1) c-Jun-N-terminal kinase activator protein 1, and (2) IκB kinase β (IKKβ)-nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB).[38] Stimulation of NF-κB upregulates genes encoding certain cytokines, such as TNF-α and IL-6. Although the appropriate amount of these cytokines is necessary for immune response, excessive stimulation can lead to the accumulation of these cytokines, thereby

contributing to diseases.[68] Macrophages also play important roles in regulating mediators of the inflammatory response, such as nitric oxide, prostaglandin E2, cyclooxygenase 2, and mitogen-activated protein kinases.[67]

Although the anti-inflammatory effect of cocoa has been demonstrated,[7,41,69] not many studies have examined the effect of theobromine on inflammation. Gu et al[20] emphasized that theobromine suppresses NF-κB activation induced by IL-1β and exerts its anti-inflammatory effect through this mechanism. Theobromine has inhibitory effects on the stimulation of TNF-α, IL-1β, IL-8, IL-6, IL-10, and monocyte chemotactic protein-1.[9,16,17,20,21,23,43] Contrary to the findings of the aforementioned studies, Lee et al[67] demonstrated in their study using RAW 264.7 macrophage cells that theobromine induced inflammatory activity by stimulating NF-κB activation and mitogen-activated protein kinase phosphorylation, resulting in the release of IL-6 and TNF-α. Camps-Bossacoma et al[9] observed that hepatic NF-κB and TNF-α expression was higher in the group of mice treated with theobromine.

Although numerous studies have proposed that theobromine possesses anti-inflammatory properties, others have indicated its potential for eliciting pro-inflammatory effects under specific circumstances. The inconsistency in findings may stem from variations in study design, dosage regimens, or the models used. Further research is warranted to elucidate these effects comprehensively. Although a definitive conclusion was not reached in the studies, it is observed that theobromine may have a positive effect on inflammation resulting from macrophage infiltration and the overall inflammatory condition.

Theobromine and Antioxidant Effect

The inflammatory process induced by obesity increases reactive oxygen species (ROS) production and oxidative stress.[70] Reactive oxygen species in our bodies are generated both endogenously and exogenously. Endogenously, they are produced by cellular organelles such as mitochondria, peroxisomes, and endoplasmic reticulum, which have high oxygen consumption rates. Exogenously, ROS are formed through various biological systems.[71] Under normal circumstances, ROS can be removed from our bodies without causing oxidative damage. However, when antioxidant defense systems are overwhelmed, oxidative damage occurs in proteins, DNA, and lipids found in mitochondria.[72] The increased nutrient intake in obesity leads to an overload on the Krebs cycle and mitochondrial respiration. As a result, mitochondrial dysfunction occurs, leading to increased ROS production.[70] Oxidative stress is a result of an imbalance between ROS production and the antioxidant defense system.[73] Oxidative stress leads to disruption in adipogenesis, stimulation of insulin resistance, and hypertrophy of adipocytes.[74]

Various antioxidant enzymes, such as superoxide dismutase, catalase, glutathione reductase, and glutathione peroxidase, are present in our bodies to alleviate oxidative stress.[72] Obese individuals have lower levels of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, in their erythrocytes.[75] In obesity, conditions such as hyperglycemia, increased blood lipid levels, vitamin and mineral deficiencies, chronic low-level inflammation, endothelial dysfunction, hyperleptinemia, impaired mitochondrial function, and dietary patterns can contribute to and exacerbate the formation of oxidative stress.[76] Obesity-induced oxidative stress can contribute to the development of various diseases, including cancer, cardiovascular diseases, neurological disorders, respiratory diseases, kidney diseases, and rheumatoid arthritis.[77] Nonenzymatic antioxidant defense systems, such as antioxidants (eg, vitamin E, polyphenols, carotenoids) become increasingly important in obesity.[78]

Consumption of cocoa decreases oxidative stress levels.[79] Additionally, studies have demonstrated the antioxidant properties of theobromine.[16,17,20,24,80–82] Theobromine decreases ROS production induced by IL-1β and reduces levels of malondialdehyde, which indicate membrane lipid peroxidation.[20] Bhat et al[16] observed that the levels of glutathione increased in mice administered theobromine, whereas the amount of thiobarbituric acid reactive substances, indicating lipid peroxidation, decreased. Papadimitriou et al[24] observed a decrease in markers of oxidative stress in the kidneys when they administered theobromine to hypertensive rats for 12 weeks. Although there is a limited number of studies on this topic, it appears that theobromine could potentially be implemented in dietary recommendations to reduce oxidative stress; however, further research is needed in this area.

CONCLUSION

When the potential effects of theobromine on obesity, inflammation, and oxidative stress are examined, it is evident that it could play a significant role in combating obesity. Theobromine contributes to the regulation of body weight, reduction of inflammation, and alleviation of oxidative stress through various mechanisms. Particularly by promoting WAT browning and eliciting anti-inflammatory responses, it holds potential for improving metabolic health. However, due to some inconsistencies in the current findings, a more comprehensive understanding of the exact mechanisms of action of theobromine through clinical trials is necessary. Current evidence supports the consideration of theobromine as a potential therapeutic agent in the fight against obesity and related metabolic disorders. Future

research should prioritize conducting large-scale clinical trials to evaluate the efficacy and safety of theobromine as a therapeutic approach for obesity. Furthermore, exploring the synergistic effects of theobromine in conjunction with other dietary components could yield valuable insights and potentially amplify its therapeutic benefits.

Author Contributions

Z.G. and D.T.A. conceived of and designed the study, wrote and revised the manuscript, and approved the version of the manuscript for submission.

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Conflicts of Interest

None declared.

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